THESIS

FOR THE AWARD OF DEGREE OF

DOCTOR OF MEDICINE

SESSION 2020-2023

A RANDOMISED COMPARATIVE STUDY BETWEEN ONDANSETRON AND ONDANSETRON WITH DEXAMETHASONE IN COMBINATION FOR PREVENTING POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPROSCOPIC CHOLECYSTECTOMY.

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"We must find time to stop and thank the people who make a difference in our lives."

- John F. Kennedy

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I cherish my association with Department of Anaesthesia And Critical Care, Santosh Medical College and Hospital, Ghaziabad

Dr. Vashist Raj

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INTRODUCTION

Laparoscopic cholecystectomy, a minimally invasive surgical procedure that has replaced the open technique for removal of a diseased gallbladder since 1990 is now one of the most common abdominal surgical procedures that is being performed especially in United states (1). Since then laparoscopic cholecystectomy is a normal procedure for the treatment of acute and chronic cholecystitis, symptomatic cholelithiasis, biliary dyskinesia, acalculous cholecystitis, gallstone induced pancreatitis, and gallbladder masses/polyps (2) with an exclusion of gallbladder cancer treatment where open radical cholecystectomy is considered to be the best option.

Laparoscopic Cholecystectomy" is considered the "**Gold Standard**" option for treatment of Gallbladder stones because of the lesser time taken for the procedure, fewer complications with minimal post-operative pain and less medications, shorter hospital stay, minimal rate of wound infection, early return to work, satisfactory cosmetic outcome.

Complications:

Almost on all patients with symptomatic gallbladder disease, laparoscopic cholecystectomy is considered to be the safe and effective procedure. However the intraoperative and immediate post-operative complications could not be ignored. The common intaoperative complications are common bile duct injury , bowel injury , injury to vascular and visceral structures. The other complications includes pain , post-operative nausea and vomiting (PONV), where the incidence of PONV could be typically seen after laparoscopic surgeries (3) with 70% of cases (4). Stimulation of mechanoreceptors in the gut by the pneumoperitoneum might be the cause for post-operative PONV (5).

Post-operative nausea and vomiting (PONV) are the two most common and unpleasant side effects that are mostly experienced by the patients following the anaesthesia and surgery. Generally nausea is a sensation of disagreeable feeling that could be experienced in the back of throat and/or epigastrium, which may or may not eventually end with vomiting (6). Forceful expulsion of contents from the stomach, duodenum or jejunum through the oral cavity is termed as vomiting (7). It is reported that the overall incidence of PONV to be around 20 to 30% (20) that might peak up to 70% in high risk patients (8) Studies earlier have

reported that pain and PONV are amongst the commonest cause for morbidity after anaesthesia and surgery (9).

Well established risk factors to PONV includes the female gender , non smoking status , past history of PONV or motion sickness , younger age group , obesity .(10). Additionally, the type of surgical procedures, use of opioids and nitrous oxide were also identified as the other predisposing factors of PONV (11). Certain surgeries which more prone for PONV inlcudes , laproscopic surgeries , gyanecological surgeries , middle ear surgeries , squint surgery. (12).

In Laparoscopic surgery , factors which are believed to contribute are rigorous decompression of abdomen by surgeon, (13) irritation of parasympathetic nerve endings in the abdomen and effect of carbon di oxide on emetic centre (14).Several studies have also reported that about 50 to 70% of patients, in absence of prophylaxis, undergoing laparoscopic cholecystectomy may develop PONV(15).

Although PONV is almost self limiting and non fatal . Adequate number of studies have reported that the incidence of PONV could be reduced with the use of various antiemetic interventions and which could improve patients' satisfaction and reduce the time to recovery and hospital stay as well (16). However, drugs to eliminate PONV is still a wonder as incidences of significant PONV is still present. The major issue in overcoming this obstacle is due its multifactorial aetiology. The factors involved are not only numerous but also so diverse and often unavoidable such that a multiple pharmacological approach needs to be devised to counter PONV rather than a single therapeutic agent. The antiemetic drugs usage remains to be the main form and plays an important role in prevention and treatment of PONV therefore, it is essential to the patients those who are at risk of developing PONV to receive prophylactic dose of multiple antiemetic drugs.

Some of the most commonly used antiemetics such as Promethazine, Metoclopramide and Droperidol could induce adverse drug effects including dry mouth, sedation, hypotension, trachycardia, extrapyramidal reactions, dystonic effects and restlessness. Quite interestingly it has been reported that Ondansetron, a 5HT3 receptor antagonists are devoid of any of these above mentioned side effects. Muscarinic M1, Dopamine D2, Histamine H1, Serotonin 5HT3 and subatnce P NK- 1 are the five principal neurotransmitter receptors that mediate nausea and vomiting (24). Furthermore, it is also reported that serotonin receptors are found in the chemoreceptors trigger zone and GI tract, hence serotonin plays a vital role on PONV(17).

A potent and highly selective long acting glucocorticoid named “Dexamethasone” that inhibits serotonin in the gut and release of endorphins are reported to augments the efficacy & reduce the side effects of other antiemetics.

Regardless of the newer generation antiemetic prophylactic use, more than 50% of surgical patients are experiencing postoperative nausea and 30% of patients are experiencing vomiting (18). The authors have also reported that in high-risk patients the incidence of PONV could more than 70%. Nauseating effects of anaesthesia is one of the most common fears of individuals undergoing surgery. Despite of postoperative pain of the patients, it is often more discomfort with the PONV (19). Prolonged PACU and hospital stay resulted in a significant increase in healthcare costs are reported to cause due to the unresolved PONV (20). Moreover, PONV is commonly associated with worsened postoperative quality of life when those with PONV rated quality of recovery at 49% vs. those without PONV at 94% (21).

Sample Size Calculation

Using formula for proportions (n) = $2(Z\alpha + Z1\text{-}\beta)^2 \times p \times q / d^2$

- In reference to my article - L. LÓPEZ-OLAONDO, F. CARRASCOSA, F. J. PUEYO, P. MONEDERO, N. BUSTO AND A. SÁEZ - Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. British Journal of Anaesthesia 1996; 76: 835–840.

Z_α = 1.96 at 5% level of significance.

Z1-β = 0.84 with 80% power

P_1 is Proportion of reference group = 24

P_2 is Proportion of the test group = 4

p = $P_1 + P_2 /2 = 28/2 = 14$

q = 1 – p (as in proportions) = 100 – 14 = 86

d is Effect size = $P_1 - P_2 = 20$

After taking dropout rate 10% , n = 47.1

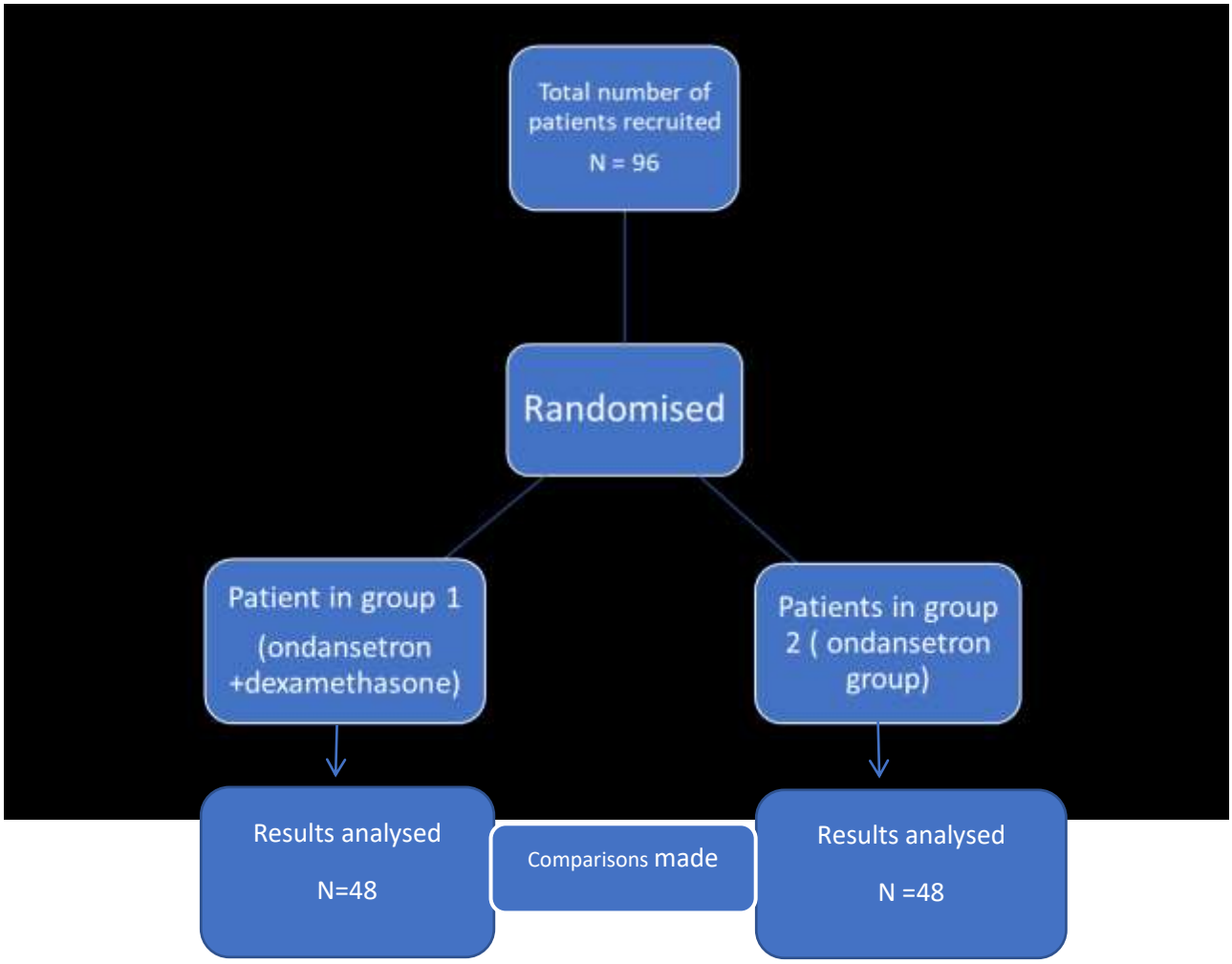
n= mean of test group, thus n= 47.1 each group.

Thus Taking n = 48

Total = n x 2 = 96

By using the above-mentioned parameters, the minimum required sample size would be 48 subjects in each of the two study groups.
Hence total of 96 subjects were included in the final analysis.

Flow chart of study design



AIMS / OBJECTIVES OF THE STUDY

AIM:

The aim is to compare the efficacy of intravenous ondansetron (4mg) and ondansetron(4mg) & dexamethasone (8mg) in combination for preventing the incidence of postoperative nausea & vomiting (PONV), in patients undergoing laparoscopic cholecystectomy.

OBJECTIVE:

To compare the two groups and see for the incidence of PONV.

- To compare the incidence of adverse effects in the two groups.
- Assessment of postoperative analgesic requirements.

Dexamethasone has antiemetic property as well act as anti inflammatory property. Ondansetron just has antiemetic property. Giving ondansetron in combination with dexamethasone is expected to provide pain relief & calming effect apart from controlling PONV.

During the follow up period of 24 hours after anaesthesia/surgery - Incidence of nausea and vomiting, Heart rate, Blood Pressure, Respiratory rate and will be monitored and recorded.

REVIEW OF LITERATURE

Frequently reported symptoms after Laprsocopic cholecystectomy are pain, postoperative nausea and vomiting (PONV), inability to ambulate and fatigue (22). The International Association for the Study of Pain (23) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". Pain can also be defined as "the normal predicted physiological response to , thermal , mechanical or adverse chemicalor stimulus associated with surgery, trauma or an acute illness and, thus, characterize it as a sensory response" (24). Pain can affect emotional, social, familial, occupational and physical functioning.

PONV are common clinical postoperative symptoms following Laproscopic cholecystectomy (25). Incidences of PONV within 24 hours after LC have been reported to occur in 20-30% (26) and might peak upto 70% in high risk patients. PONV are distressful experiences for patients that may not only delay discharge from hospital but also lead to dehydration, electrolyte imbalance (27), suture dehiscence (28) and oesophageal rupture (29). Furthermore, patients have an increased risk of haematoma formation and aspiration pneumonitis due to the depression of airway reflexes postoperatively (30).

Review of Laparoscopic Cholecystectomy and PONV:

The problem of nausea and vomiting is not new, but very old and a less thought of problem. Before any specific anti-emetic agents became available, various techniques, including olive oil and insulin glucose infusions were reported to be effective in reducing the incidence of postoperative nausea and vomiting. The use of olive oil was described in 1912 (31). The oil was administered by mouth immediately after partial restoration of consciousness and he postulated that oil in the stomach absorbed any ether that might be there. But effect of Atropine was appreciated by Brown - Sequard as early as 1883 when he discovered that addition of atropine to morphine prevents nausea and vomiting.

A score was developed in 1999 for risk stratification of postoperative nausea and vomiting (PONV) called as Apfel simplified risk score. It is the most widely used tool for risk stratification. With 1 point present chances of PONV increases by 10-20% , with 2 points risk increases by 20-40% , with 3 points risk rises to40- 60% and with 4 points risk rises to 60-80%.

Apfel simplified risk score

Sl.No	Risk factors	Points
1.	Female Gender	1
2.	Obesity	1
3.	Non smoker	1
4.	History of PONV	1

Pharmacological therapies used for Treatment of Nausea and Vomiting:

	Generic name	Mode of administration	Dose (mg)	Timing of administration
First class	Dexamethasone	I.V.	4–8	Induction
	Droperidol	I.V.	0.625–1.25	End of surgery
	Ondansetron	I.V.	4	Induction
	Palonosetron	I.V.	0.075	Induction
	Aprepitant	Oral	40	Before induction
Second class	Dimenhydrinate	I.V.	50	Induction
	Scopolamine	Transdermal	1	The night before/day of surgery
	Metoclopramide	I.V.	25–50	Induction

First class antiemetic interventions

Three classes of antiemetic drugs that is serotonin antagonists (e.g. ondansetron), corticosteroids (e.g. dexamethasone), and dopamine antagonists (e.g. droperidol) have similar efficacy against PONV, with a relative risk reduction of around 25%. Moreover, they act independently and, when used in combination, have additive effects.

The 5HT3 antagonists like Ondansetron is a proven effective agent not only in the management of Post-Operative Nausea and Vomiting and but also in emesis due to cancer chemotherapy. These drugs act by being highly selective and potent antagonist of 5HT3 receptor in the brain (Area postrema and nucleus tractus solitarius) and peripherally in the gastro-intestinal tract. Dexamethasone was first reported to be an effective antiemetic agent in patients undergoing cancer chemotherapy in 1981.

Three other serotonin antagonists, i.e , dolasetron, granisetron and palonosetron, have a similar efficacy and side-effect profile (e.g. constipation, headache) to ondansetron. Like droperidol, , granisetron, ondansetron and dolasetron are all associated with QTc prolongation, which increases the risk of torsades de pointes and must be avoided when patients exhibit QTc prolongation. The most recent serotonin antagonist, palonosetron, has no effect on the QTc interval and, furthermore, has a longer duration of action—up to 72 h—due to its unique 5-HT_3 receptor-binding properties. Therefore, palonosetron may be a particularly effective prophylaxis against PONV for ambulatory surgery.

The D2 receptor antagonist droperidol has a short plasma half-life and should therefore be given towards the end of surgery. Droperidol may result in sedation and QTc prolongation and has even been issued a black-box warning from the US Food and Drug Administration following reports of severe cardiac arrhythmias.

Neurokinin-1 receptor antagonists are a promising new class of antiemetics that were originally developed and approved for chemotherapy-induced nausea and vomiting. Administrated orally before surgery, aprepitant has similar efficacy against nausea and greater efficacy against vomiting compared with other commonly used antiemetics. In fact, in two randomized controlled trials, aprepitant decreased the incidence of vomiting by 70–80%. Aprepitant is not associated with QTc prolongation or sedative effects, but its high cost limits its use to high-risk patients.

Second-line antiemetic interventions:

The following drugs are characterized by less favourable side-effect profiles or limited evidence of efficacy.

Metoclopramide is widely used D2 antagonist. Contrary to popular belief, the 10 mg dose has no effect on PONV, but 25–50 mg has similar efficacy compared with other antiemetics. Metoclopramide use has been associated with extrapyramidal and sedative side-effects.

Haloperidol a butyrophenone similar to droperidol. Nonetheless, precise data on optimal dosage, timing, and safety are lacking. I.V. injection is now off-label in the USA due to reports of cardiac arrhythmias and death associated with its use.

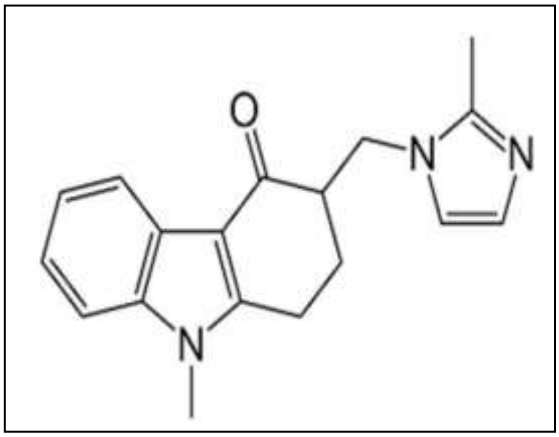
Dimenhydrinate is an antihistamine like promethazine and cyclizine. There are few randomized controlled trials investigating its use for PONV, and the drug is associated with a significant rate of side-effects like sedation, dry mouth, visual disturbance, and urinary retention.

Transdermal scopolamine is a cholinergic antagonist typically used to treat motion sickness. A recent meta-analysis showed a 40% risk reduction in PONV, but a three-fold increase in visual disturbance, compared with placebo when transdermal scopolamine is administered the night before or the day of surgery.

An alternative to pharmacological treatment may be acustimulation of P6, which has demonstrated some efficacy in reducing PONV without major side-effects. Some uncertainties remain regarding the type of stimulation to apply, the timing, and the target population.

Ondansetron:

Ondansetron, generally referred as “Zofran,” that was developed and studied in the 1980s and is widely approved now as antiemetic drug and is being used as one of the preventing and treatment options for patients suffering from nausea and vomiting associated with chemotherapy, radiation therapy, and surgery (32).



Molecular Structure of Ondansetron

Chemistry of Ondansetron:

Ondansetron is a synthetic compound having an indole nucleus similar to the structure of 5-HT3. The compound has one asymmetric centre and is a **1:'1** racemic mixture of both the enantiomers D and L forms with selective 5-HT3 receptors antagonistic actions. Ondansetron has a pK of 7.4 with an aqueous pH of 4.6 and is stable for four years under normal conditions.

Metabolism

The major route of clearance of ondansetron (95%) is by hepatic metabolism (33). The enzyme systems involved are on cytochrome P450, particularly CYP2D6 and CYP3A (44). Ondansetron is metabolized by hydroxylation at the indole moiety to 7 and (mainly) **8-** hydroxyondansetron, followed by glucuronide or sulphate conjugation (Saynor & Dixon 1989); 6- hydroxylation and demethylation are minor routes of metabolism. Forty percent of ondansetron is metabolized to the active compound ***8-*** hydroxyondansetron, which is not detected in plasma as it is rapidly conjugated in the liver. It does not contribute to the activity of the parent drug.

Clearance

Plasma clearance is approximately 40% of hepatic blood flow. Changes in blood flow should not change hepatic clearance. Repeated dosing for 4 days does not alter clearance, indicating that the drug does not inhibit or augment its own metabolism (35). Renal clearance of ondansetron is low; less than ***5%*** of the drug is excreted unchanged in urine. Total plasma

clearance is 600-700 mL min- and renal clearance is about 20 mL min-' after an intravenous dose (36). A review of clearance in a group of 86 healthy, young, male volunteers showed a four- to fivefold range in values (37). The area under the plasma concentration- time curve (AUC) relates directly to clearance, and may vary widely between healthy volunteers given the same dosing schedules. There is no evidence for bimodal or trimodal distribution, and, therefore, no genetic polymorphism in ondansetron clearance. No discrete groups of patients have inherently lower clearance.

Excretion

Following intravenous administration of radiolabelled ondansetron, more than 60% of its metabolites are excreted in urine. The remainder are found in faeces (38). As a lipophilic drug, which diffuses easily, ondansetron will probably pass across the placenta and into milk; there are, however, no published data on these phenomena. Ondansetron is not recommended during pregnancy and lactation

Pharmacology of Ondansetron:

Etiology of many disease states that 5-Hydroxytryptamine (5-HT, serotonin) is a monoaminergic neurotransmitter that modulates numerous neuronal functions (39). It is specifically important in cases of mental health illness patients those who are suffering from depression, anxiety, schizophrenia, eating disorders, obsessive compulsive disorder, panic disorders, migraines, etc. Physiologically, it helps in modulating the contraction and relaxation of smooth muscles in the respiratory & gastrointestinal tracts and blood vessels, platelet plug formation during haemostasis, provocation of pain, induction of vomiting, precipitation of mood changes and induction of sleep (40). Other physiological effects of 5-HT would also be produced by interacting with various 5-HT receptor subtypes 1 through 5 (41).

5-HT3 receptors, a serotonin-gated ion channel that is selectively permeable to the ions namely Na^{+}, K^{+}, and Ca^{++} ions those involved in the process of depolarization. The effects of ondansetron in different disorders may be attributed based on the wide distribution of 5-HT-3 receptors and their role in different organs. However, relatively high concentration of 5-HT-3 receptors are found in the areas such as postrema (chemoreceptor trigger zone), nucleus tractus solitaries (vomiting centre), sub-stantia gelatinosa (at all levels, nuclei of the lower brain stems, such as trigeminal nucleus and the dorsal vagal complexes and in the spinal cord (42). In addition, 5-HT 3 receptors are linked with several other neurotransmitters, including norepinephrine, acetylcholine, cholecystokinin, g-aminobutyric acid (GABA), glycine, and dopamine (43).

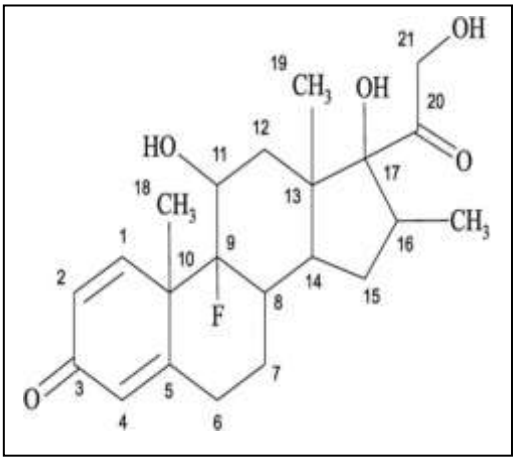
Mechanism of Action:

IT is well known that chemoreceptors, including dopamine, histamine, serotonin, and acetylcholine are abundant in the vomiting centre of human brain. Therefore, it is quite common that drugs designed to block the uptake of these chemicals have the capacity to minimize nausea and vomiting. One among those drugs are the Ondansetron and the other members of the –setron family are the serotonin antagonists, which means the one that blocks the serotonin receptors in the chemoreceptor trigger zone (CTZ) within the medulla oblongata. Its normal that initiation of vomiting will be started once the vomiting centre receives the signals from CTZ. Such communication of the CTZ to vomiting centre will be decreased by blocking the serotonin receptors and thereby minimizing the entry of serotonin to the CTZ, thus the patient experiences reduced nausea and vomiting.

Adverse drug reactions (ADR) for ondansetron can include headache, dizziness, constipation, and/or diarrhoea. Some patients also experience drowsiness after taking ondansetron. Some medical providers feel that this side effect is not caused by the drug itself, but rather the patient is feeling better and able to rest. While taking ondansetron, some patients may have increased liver enzyme levels. These levels usually return to normal when the patient stops taking the medication. Rarely, ondansetron can cause cardiac arrhythmias, or abnormal heart rhythms, such as long QT syndrome.

Dexamethasone:

Dexamethasone, a well-known synthetic glucocorticoid with minimal mineralocorticoid activity is one of the primarily used anti-allergic and anti-inflammatory drugs (44) with 30 to 40 times more potent of hydrocortisone and is almost sixteen times potent than prednisolone. It has been reported that dexamethasone and its related glucocorticoids effective drugs for preventing nausea and vomiting due to various conditions including chemotherapy-induced nausea and vomiting (CINV) (45), radiotherapy-induced nausea and vomiting (RINV) (46) and postoperative nausea and vomiting (PONV) (47). The Society of Ambulatory Anesthesia (SAMBA), based on the international guidelines, has recommendedDexamethasone for preventing PONV (48).



Molecular Structure of Dexamethasone

Pharmacodynamics:

Dexamethasone bind to the glucocorticoid receptors and thereby inhibits pro-inflammatory signals and promoting anti-inflammatory signals with wide range of therapeutic window based on the patients' requirements. It is also specified that patients receiving corticosteroids should be counselled for the risk of hypothalamic-pituitary-adrenal axis suppression and further increased susceptibility to infections.

Metabolism:

Dexamethasone, a 6-hydroxylated, would be converted into 6α- and 6β-hydroxy dexamethasone (49), which be irreversibly metabolized to 11-dehydrodexamethasone by corticoids 11-β-dehydrogenase isozyme 2 that also converted back by the corticosteroid 11-β-dehydrogenase isozyme 1 to dexamethasone (50).

Half-life, Elimination and Clearance:

Half-life of dexamethasone has been determined to be 4 hr when it is used as 20 mg oral tablet with a clearance of 15.7l/h and for 1.5mg oral dose has 6.6±4.3h with a clearance of 15.6±4.9l/h, whereas a 3.0mg intramuscular dose has 4.2±1.2h with a clearance of 9.9±1.4l/h (51). Even though urine is the general predominant route of elimination for corticosteroids, dexamethasone elimination in the urine is reported to be <10% (52).

Mechanism of Action:

Dexamethasone is bound to plasma proteins in much lower-levels than other glucocorticoids. Hepatic metabolism (both glucuronidation and sulfation) occurs to produce inactive metabolites, with 65% of the dose of dexamethasone excreted in the urine within 24 hours, with less than 3% unchanged. It is regarded as one of the ideal peri-operative agent being readily available, cheap, anti-inflammatory agent, prevents and treats post-operative nausea

and vomiting (PONV), promotes appetite, suppress inflammation, a good analgesic agent both as intravenously or as an adjuvant to peripheral nerve blocks, it provides a sense of well-being and is considered to have a good quality of recovery and early discharge in patients from anesthesia. It has a complex mechanism of action involving binding of steroid ring to the receptor effect site, which results in gene transcription, and resulting in decreased release of mediators like bradykinin, IL 1, 2 and 6, resulting in pain relief.

Pharmacology of Dexamethasone and its Role in PONV:

The mechanism of action of dexamethasone as an antiemetic agent, is unknown.There are various postulated mechanism is depletion of γ-aminobutyric acid (GABA) stores, and reduction of blood brain barrier to emetogenic toxins, inhibition of central prostaglandins and serotonin. There are tremendous literature available which suggest that dexamethasone reduce the incidence of post-operative nausea and vomiting. In one of the biggest DREAMS trial collaborators, 1350 participants were randomly allocated to dexamethasone and control group, and it was found that a single dose of 8 mg dexamethasone reduced the incidence of nausea and vomiting till 24 hours and rescue anti-emetics were not required till 72 hours in patients who underwent bowel surgeries with no adverse events (53).

Vlok found that there is a significant reduction in post-operative nausea and vomiting and post-operative pain as compared to tramadol, pethidine, magnesium sulphate and tramadol (54). Sekhavat et al suggested that a single prophylactic dose of dexamethasone 8 mg after an operation can reduce postoperative nausea and vomiting (55). Narayanappa et al suggested that combination of dexamaethasone and ramosetron is more effective than palonosetron in PONV prevention, and they did their study in gynecological surgeries under spinal anesthesia (56). While there were researchers who were publishing astonishing results of dexamethasone as a good prophylactic and therapeutic agent for PONV, there were concerns which were raised suggesting the risk of surgical site infections. Kurz et al in the year 2015 did investigations and found that a single dose of dexamethasone used in peri-operative period does not increase the risk of surgical site infections (57). However, the combination of dexamethasone and ondansetron was not effective in preventing PONV or severe PONV in obese patients undergoing laparoscopic sleeve gastrectomy after titrated total intravenous anesthesia (TIVA) (58).

Studies On Postoperative Nausea & Vomiting:

LÓPEZ-OLAONDO et al., in the year 1996 (59) : conducted a study on Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. It was concluded that ondansetron as well as dexamethasone alone provided adequate control of ponv. But the combination group (Ondansetron + Dexamethasone) was most effective in reducing PONV.

Bhattarai B et al (2011) (60)**:** did a comparison of ondansetron alone and combination of ondansetron and dexamethasone as a prophylaxis for postoperative nausea and vomiting in adults undergoing elective laparoscopic surgery in his study. He concluded from this study that the combination of ondansetron 4 mg with dexamethasone 4 mg is more effective than ondansetron 4 mg alone in preventing PONV.

B.Subramaniam et al (2001) (61)**.** Did study that Dexamethasone is an cost-effective alternative to ondansetron in preventing PONV after pediatric strabismus repair. The result suggested that the incidence of PONV in early postoperative period (0-6hr) was almost similar, but the incidence of PONV in late postoperative period (6-24hr) was significantly lower in dexamethasone group.

Mohan L et al., in the year 2004 (62):Studied to compare the efficacy of intravenous ondansetron and dexamethasone for prevention of post-operative vomiting in pediatric patients whom underwent intra-abdominal surgery at Indira Gandhi institute of medical sciences, Patna. It was observed that single dose ondansetron 0.1 mg/kg and dexamethasone 0.5 mg/kg, given intravenously are equally effective agents for the control of PONV. Both drugs for the same indication do not seem to increase the antiemetic efficacy.

Areen Fatima et al., in the year 2016 (63): conducted a comparative Study of Efficacy and Safety of Ondansetron, Glycopyrrolate and Dexamethasone for Postoperative Nausea and Vomiting Following General Anesthesia. It was concluded that the prophylactic use of ondansetron and glycopyrrolate was more effective with fewer side effects in reducing the incidence of nausea and vomiting postoperatively than with dexamethasone.

Suman Chattopadhyay et al., (2016) (64):Laparoscopic cholecystectomy is associated with an appreciably high rate of postoperative nausea & vomiting (PONV) which is considered as a reason of patient's delay in discharge and disability aggravation. This study was designed to compare the effectiveness of Ondansetron, Dexamethasone and Ondansetron plus Dexamethasone as an antiemetic prophylaxis for preventing PONV in patients after laparoscopic cholecystectomy. It was concluded that the combination of Dexamethasone and Ondansetron is better than each drug alone as an antiemetic prophylaxis against PONV following laparoscopic cholecystectomy.

Dalhat and Mohammad in the year 2018 (65): have designed and conducted a prospective study to compare the efficacies of ondansetron and metoclopramide in preventing the postoperative nausea and vomiting after day-case gynecological laparoscopic surgeries. A total of sixty-six ASA I and II patients aged between 18 to 55 years old those who gave their consent were involved in to the study and randomly allocated in to either one of the groups who receive either 4 mg of intravenous injection of either ondansetron or metoclopramide 10 mg intravenous prior to the induction of anesthesia. On observation for up to 4 hr the authors have reported that ondansetron offered a significant prophylaxis against PONV compared to metoclopramide in patients undergone with gynecological laparoscopic surgery.

Debasmita Jash et al., (2019) (66): conducted a comparative study between Ondansetron and Dexamethasone for Preventing Postoperative Nausea and Vomiting after laparoscopic Cholecystectomy. They observed that Ondansetron is as effective as Dexamethasone in reducing the incidence of post-operative nausea and vomiting in laparoscopic cholecystectomy with minimal side effects. Use of rescue antiemetic is same with Ondansetron as well as Dexamethasone. From this study, we can conclude that Ondansetron, a 5-HT3 antagonist, in a dose of 4 mg and Dexamethasone, a glucocorticoid, in a dose of 8 mg are both effective prophylactic drugs in the prevention of PONV in laparoscopic cholecystectomy under general anesthesia.

Sridharan and Sivaramakrishnan in the year 2019 (67): conducted a meta-analysis study to analyze the effective drugs that are being used to prevent postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy by including the randomized trials and trial sequential analysis and the authors have reported that dexamethasone and ondansetron have been evidenced as the stand alone options and the combination of both is preferred in cases of high-risk category.

Shivanna AD et al (68): conducted a randomized controlled trial to compare the anti-emetic efficacy of Ondansetron with Ondansetron with Dexamethasone Combination Therapies in Women Undergoing Breast Surgeries:

Som A et al (2016) (69): Did a meta-analysis - Combination of a 5-HT3 receptor antagonist and dexamethasone is significantly more effective than 5-HT3 antagonist alone in preventing PONV after laparoscopic surgeries, with possible improvement in postoperative analgesia.

McKenzie R et al (1994) (70): conducted a study to compare ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting.He found out that the combination of ondansetron and dexamethasone was more effective than ondansetron and saline in the prevention of postoperative nausea and vomiting for women having major gynecologic surgery.

Materials & Methods

Study Design: Randomised comparative Study.

Organisation of study: Santosh Deemed to be University, Ghaziabad

Place of study: Department of Anaesthesiology, Santosh Hospital, Ghaziabad

Duration of study: 1 year

Study Population: Patients admitted for Laproscopic cholecystectomy procedure under General Anaesthesia with controlled ventilation were taken up for study. Institutional Ethics Committee Approval & Informed Patient Consent has been obtained from the Institutional Ethics Committee of Santosh Deemed to be University before starting the study.

Study groups:

Group 1 – Patients receiving iv. Ondansetron 4mg + Dexamethasone 8mg (n= 48)

Group 2 – Patients receiving iv. Ondansetron 4mg (n = 48)

INCLUSION CRITERIA:

1. Written informed consent by the patient's relative
2. ASA risk I and II.
3. Patients aged between 18-65yrs.
4. Patients scheduled for laparoscopic cholecystectomy under general anaesthesia.

EXCLUSION CRITERIA:

1. Patient refusing to give consent
2. Allergy
3. Patients with renal impairment, hepatic disease, neurological and endocrinal abnormalities were excluded.
4. ASA status III, IV, V

5. Emergency surgeries

This study was undertaken at the Santosh Medical College & Hospital during the year 2021-2022.

After obtaining approval from institutional ethics committee of Santosh Deemed to be University, and taking the informed consent from the patients, 96 adult patients of either sex belonging to ASA grade I and grade II admitted to Santosh Hospital, Ghaziabad, for laparoscopic cholecystectomy under general anaesthesia were randomly divided into 2 groups, 48 in each group.

Group 1: Patients intravenously injected with Ondansetron 4mg + Dexamethasone 8mg.

Group 2: Patients intravenously injected with Ondansetron 4mg.

PREANESTHETIC CHECKUP:

A thorough pre anaesthetic examination was done a day before the surgery and written informed consent was taken from all the patients. Physical examination of all patients as also done. Airway examination including MPG grading, Mouth opening was done. All patients under exclusion criteria will be excluded from the study. All routine haematological, biochemical & radiological investigations, electrocardiogram appropriate for the surgery were done. A preoperative visit arranged to allay the anxiety and to develop a good rapport. The patients was instructed to fast overnight and aspiration prophylaxis was advised with iv./tab Rantac150 mg and Tab alprazolam 0.25 mg night before surgery. Visual Analogue Score (VAS) was explained to all the patients and information was given regarding pain scoring system ranging from 0 to 10 for determination of severity.

METHOD

On the day of surgery, the patients were examined in the preoperative room and the pulse rate (PR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded and the mean arterial pressure (MAP) was calculated as preoperative value. Patients were randomly assigned into two groups of 48 each, GROUP 1 and GROUP 2 using a computer generated randomization chart.

Group 1: Patients intravenously injected with Ondansetron 4mg + Dexamethasone 8mg.

Group 2: Patients intravenously injected with Ondansetron 4mg.

A 18/20G Gauge intravenous cannula was placed and crystalloid infusion was started. The rate of infusion is as per the Holliday- Segar rule.

On arrival in the operating room, patients were monitored with a non- invasive multipara monitor. The parameters that were monitored includes heart rate, blood pressure, oxygen saturation, electrocardiogram, capnography. The interventional medications were procured by indenting from the hospital pharmacy and thus are identical. A standard uniform protocol for premedication drugs, induction agents, muscle relaxants, and maintenance of anaesthesia were administered in all the patients and the groups. Thereafter, the patients categorized as Group 1 have received 4mg of Ondansetron intravenous (IV) and Group 2 patients iv. Ondansetron 4mg + iv. Dexamethasone 8mg, preoperatively 1 min before induction with anaesthetic agent.

Patients have been induced with propofol 1.5-2 mg/kg^{-1} or in a dose sufficient for loss of verbal commands. Controlled positive pressure ventilation was done with 100% oxygen using bag and mask. Direct laryngoscopy and orotracheal intubation with appropriate size cuffed endotracheal tube was facilitated with vecuronium 0.1 $mg.kg^{-1}$ after 4 minutes. Anaesthesia was maintained with isoflurane and nitrous oxide 60% in oxygen and top up doses of injection vecuronium bromide 0.01mg/kg as muscle relaxant.

The patients have been mechanically ventilated using circle system to maintain the normocapnia. Anaesthetic agents have been stopped at the end of surgery. At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.05 $mg.kg^{-1}$ and glycopyrrolate 0.01 $mg.kg^{-1}$. On the recovery of the patients, they were extubated after thorough oral suctioning and taken to the post anaesthesia care unit (PACU) and further were under observation for upto 24 hours. In the PACU, patients who received Injection diclofenac sodium 1.5 mg/kg i.v was used as rescue analgesic and thereafter whenever the VAS score became ≥4.

FOLLOWING OBSERVATIONS WILL BE MADE:

Intraoperatively, HR, MAP, SBP, and DBP levels have be monitored and recorded before and after induction, immediately after intubation and 1, 5, and 10 min after laryngoscopy and endotracheal intubation, and every 15 mins intraoperatively for up to 1hour.

Duration of surgery and anaesthesia were noted. Patients have been observed for 24 hours post operatively. Nausea, vomiting, and postoperative pain have been recorded for 24 hours at 2, 6, 12, 24 hr. Discharge time from recovery room to ward was also noted. Patients were under observation for complications and treated as required.

Throughout the study, patients have been observed for any adverse effects like bradycardia, tachycardia (PR less than or more than 20% of pre-operative level respectively on two consecutive readings), hypo and hypertension (MAP less than or more than 20% of pre-operative level respectively on two consecutive readings), respiratory depression (SaO_2 < 90%), headache, diarrhoea, constipation, allergic reactions and they were managed conventionally.

Assessment:

Episodes of emesis and nausea have been recorded. Repeated vomiting within 1-2 minutes period was recorded as single emesis, the data were taken as follows: **Nausea** was measured using a 5 point numerical scale. Severe and moderate score were considered major nausea.

- 0 = No Nausea.
- > or =2 is signisficant comes in mild
- 2 & 3 = mild
- 4 = moderate
- 5 = Severe.

For Vomiting:

- If Present - Yes
- If Absent = NO

Rescue analgesic consisting 75 mg diclofenac sodium IV was given for patients those who experienced a pain score of more than 5 in the scale.

Data management and Statistical Analysis

- The data was collected and was entered in MS excel.

Statistical Analysis:

The data collected during the study was compiled using a Microsoft Excel spread sheet and analyzed statistically using the statistical package for the MedCalc statistical Software version 20.115 for window editions. Qualitative data were presented as number, percentage and Quantitative data were presented as mean±SD and median. Comparison between groups was done by $\chi 2$-test, fisher exact test, unpaired t test and Mann Whitney u test. P value less than 0.05 was considered to be statistically significant.

OBSERVATIONS AND RESULTS

Table 1: Average Age Distribution of the Patients

Age (yrs)	Group 1		Group 2	
	N	%	N	%
18-30	10	20.83	9	18.75
31-40	11	22.92	11	22.92
41-50	20	41.67	23	47.92
51-60	7	14.58	5	10.42
Median	42		42	
Range	18-60		18-57	
Mean±SD	40.87±10.05		40.66±9.05	
t & p value	0.106, 0.915 (NS)			

Unpaired t test was used.

Average Age of the Patients: A total of 96 patients were randomized into 2 groups 1 & 2 of 30 patients each and received intravenous Dexamethasone + Ondansetron combination and Ondansetron alone, respectively as PONV prophylaxis. Unpaired t test was applied. The average age of the patients in **group 1** was **40.87 ± 10.05 and in group 2 was 40.66 ± 9.05**. There was no significant difference in the average age between the two groups in the present study.

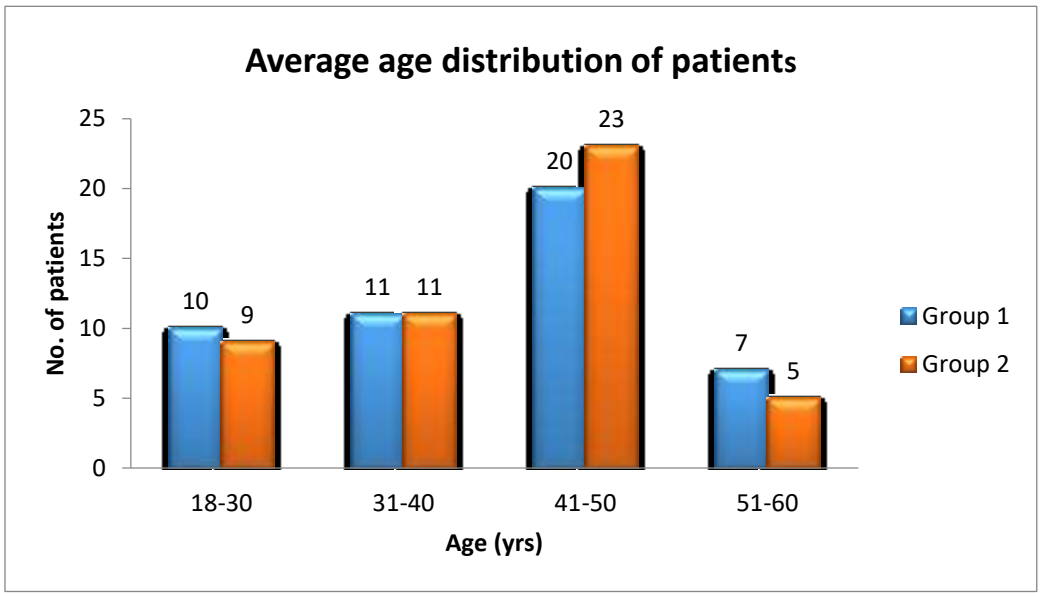


Table 2: Gender Distribution

Gender	Group 1		Group 2	
	N	%	N	%
Male	17	35.42	16	33.33
Female	31	64.58	32	66.67
Total	48	100.00	48	100.00

Chi square 0.046, P value 0.829 (NS)

Gender distribution: Both the groups were comparable in the distribution of gender such as male and female. Group 1 having **17 males and 31 females** whereas in group 2 it was **16 males and 32 females** showing no significant difference in the gender distribution between the two groups.

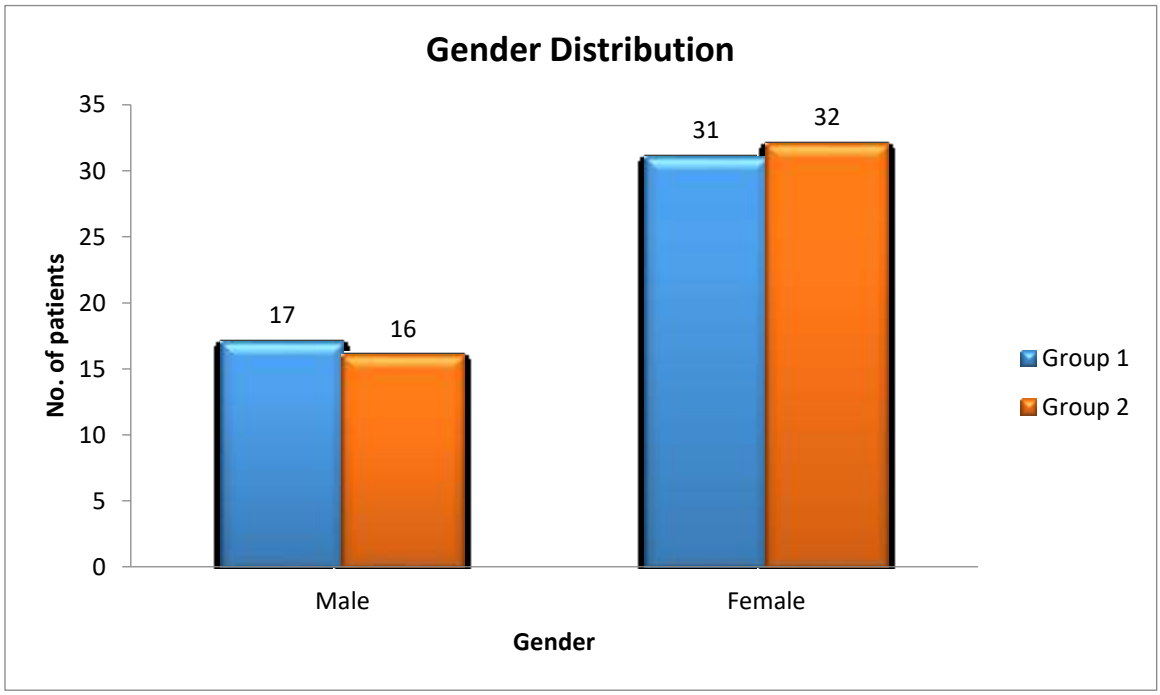


Table 3: Average Body Weight of Patients

Groups	Mean ± SD	P value
Group 1	66.08±5.67	0.3452
Group 2	65.02±5.27	

Body weight of the patients: The body weight of patients randomized into the groups were shown in table 4. The average body weight of patients belonging to both the groups 1 & 2 were found to be **66.08±5.67** and **65.02±5.27**. There was no significant difference in the average body weight in kg between the two groups. The calculated *p* values was found to 0.3452.

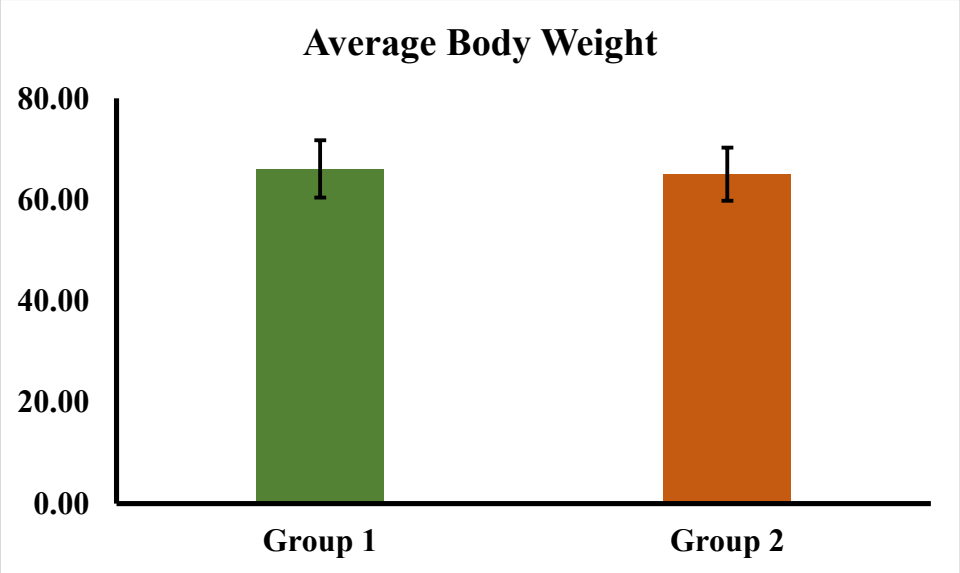


Table 4: Average BMI of the Patients

BMI	Group 1		Group 2	
	N	%	N	%
>18.5	0	0.00	0	0.00
18.5-24.9	48	100.00	48	100.00
25-29.9	0	0.00	0	0.00
≥30	0	0.00	0	0.00
Median	22		22	
Range	19-24		19-24	
Mean±SD	21.8±1.50		21.8±1.42	
t & p value	0.139, 0.889 (NS)			

Table 4 shows : Body mass index (BMI) The body mass index of patients randomized into the groups were shown in table 5. The average BMI of patients belonging to both the groups 1 & 2 were found to be **21.85±1.50** and **21.8±1.42**. There was no significant difference in the average BMI between the two groups. The calculated *p* value was fond to 0.889.

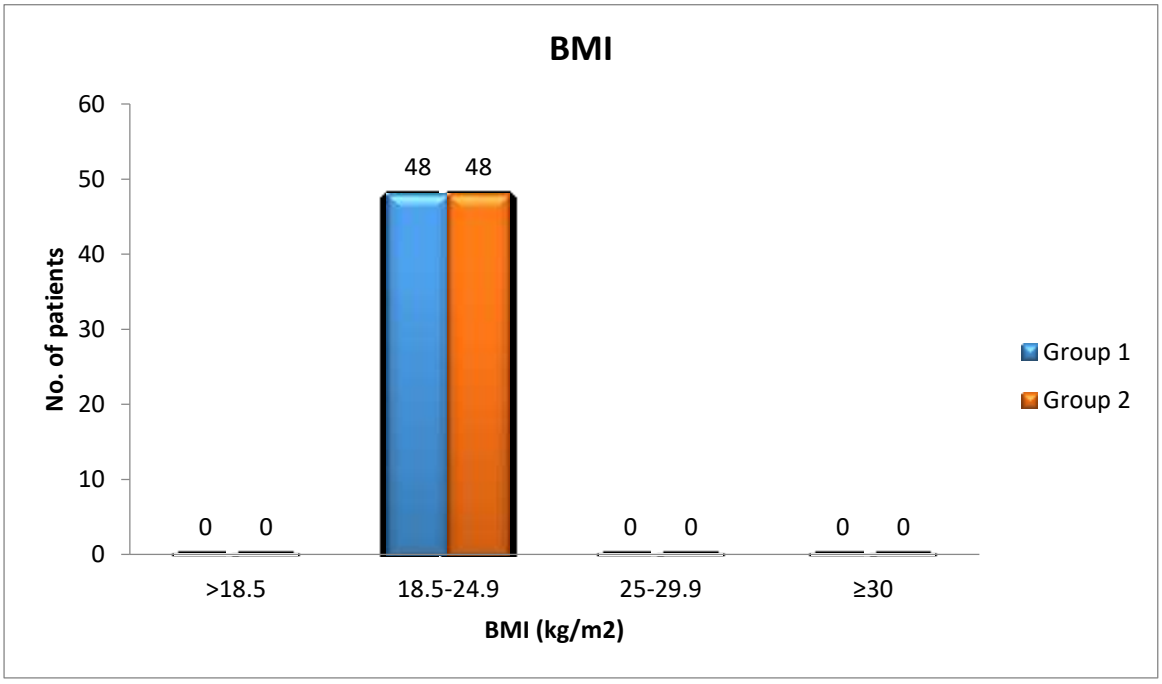


Table 5: Average of Basal level Hemodynamic and Heart Rate of Patients

Parameters	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	P value
SBP	127.10±5.70	125.13±0.0532	P = 0.0532
DBP	77.69±5.24	78.08±4.49	P = 0.6963
MAP	94.16±4.20	93.76±3.78	P = 0.6250
HR	77.52±10.01	76.38±7.64	P = 0.5320

Table 5 shows : Baseline Hemodynamic Parameters: The baseline values of the hemodynamic parameters such systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were recorded and the mean average values were calculated and tabulated in Table 7. Based on the recorded values of the SBP, DBP, MAP and HR there was no significant difference between the two groups.

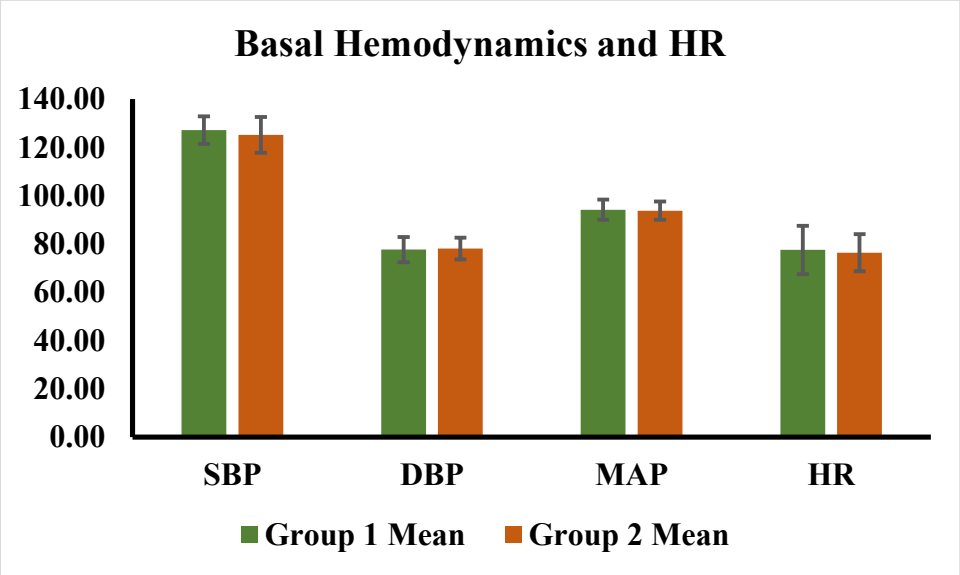
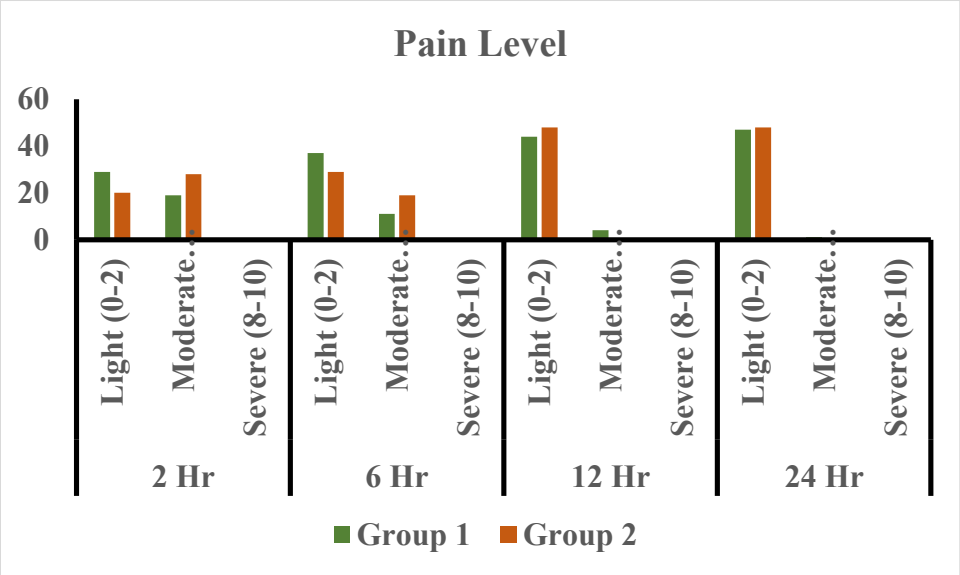


Table 6: Number of Patients with different levels of Pain Categories Based on VAS Scores at different Time points

		Group 1	%	Group 2	%
2 Hr	Light (0-2)	29	60.42	20	41.67
	Moderate (3-7)	19	39.58	28	58.33
	Severe (8-10)	0	0.00	0	0.00
6 Hr	Light (0-2)	37	77.08	29	60.42
	Moderate (3-7)	11	22.92	19	39.58
	Severe (8-10)	0	0.00	0	0.00
12 Hr	Light (0-2)	44	91.67	48	100.00
	Moderate (3-7)	4	8.33	0	0.00
	Severe (8-10)	0	0.00	0	0.00
24 Hr	Light (0-2)	47	97.92	48	100.00
	Moderate (3-7)	1	2.08	0	0.00
	Severe (8-10)	0	0.00	0	0.00

Table 6: shows the pain level experienced by the patients in both the groups 1 & 2. Number of Patients had pain has been categorized in to 3 namely 0-2;3-7; and 8-10 at different time points such as 2 hrs; 6 hrs; 12 hrs; and 24 hrs.


Pain Level
60
40
20
0
Light (0-2)
Moderate...
Severe (8-10)
2 Hr
6 Hr
12 Hr
24 Hr
Group 1
Group 2

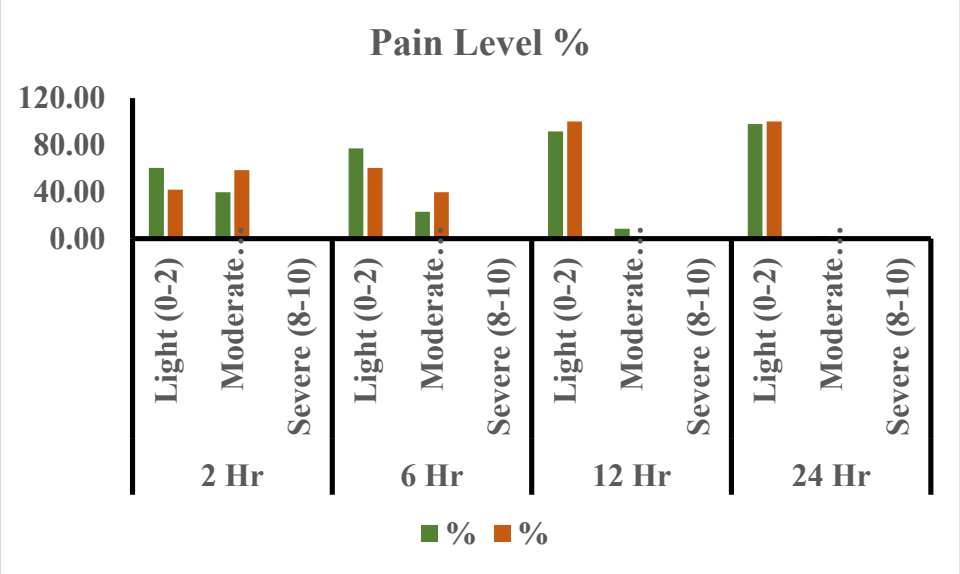

Pain Level %
120.00
80.00
40.00
0.00
Light (0-2)
Moderate...
Severe (8-10)
2 Hr
6 Hr
12 Hr
24 Hr
%
%

Table 7: Number of Patients with Experienced different levels of Nausea Categories at different Time points

Time		Nausea				p value
		Group 1		Group 2		
		N	%	N	%	
0-6 hrs	Present	6	12.50	28	58.33	**<0.0001**
	Absent	42	87.50	20	41.67	
6-12 hrs	Present	2	4.17	10	20.83	**0.027**
	Absent	46	95.83	38	79.17	
12-24 hrs	Present	0	0.00	1	2.08	1.000
	Absent	48	100.00	47	97.92	

Chi square & Fisher exact test used.

Table 7: shows the Number of Patients with experienced different levels of nausea categories at different time points. It was observed that out of the total 48patients , 6 patients (12.50%) under group 1 experienced nausea varying from light to severe between 0 to 6 hrs in postoperatively. While in group 2, 28 patients (58.33%) experienced nausea in between the time period of 0-6 hrs out of total of 48 patients in postoperative period. Further during the time period of 6-12hr , 2 patients (4.17%) out of 48 patients in group 1 and 10 patients (20.83) out of 48 patients in group 2 had nausea of varying severity. However, during the time period between 12 and 24 hrs, 100% of the patients in group 1 had no symptoms of nausea but in group 2 , 2.08 % of patients still had some degree of nausea. P value is significant during the time period of 0-6hr and 6-12 hr.

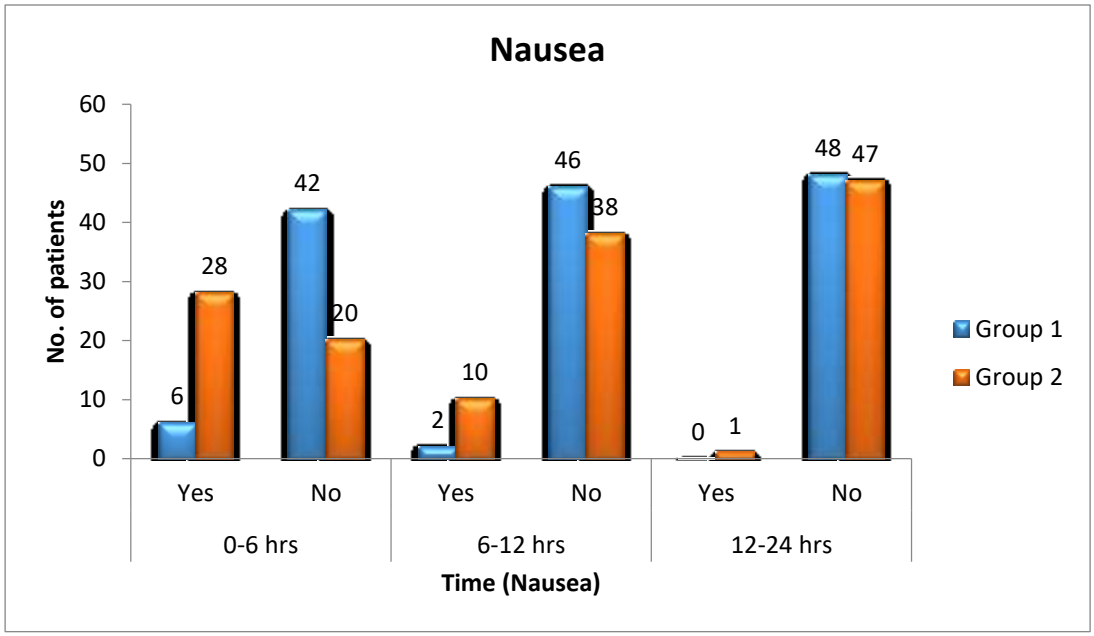
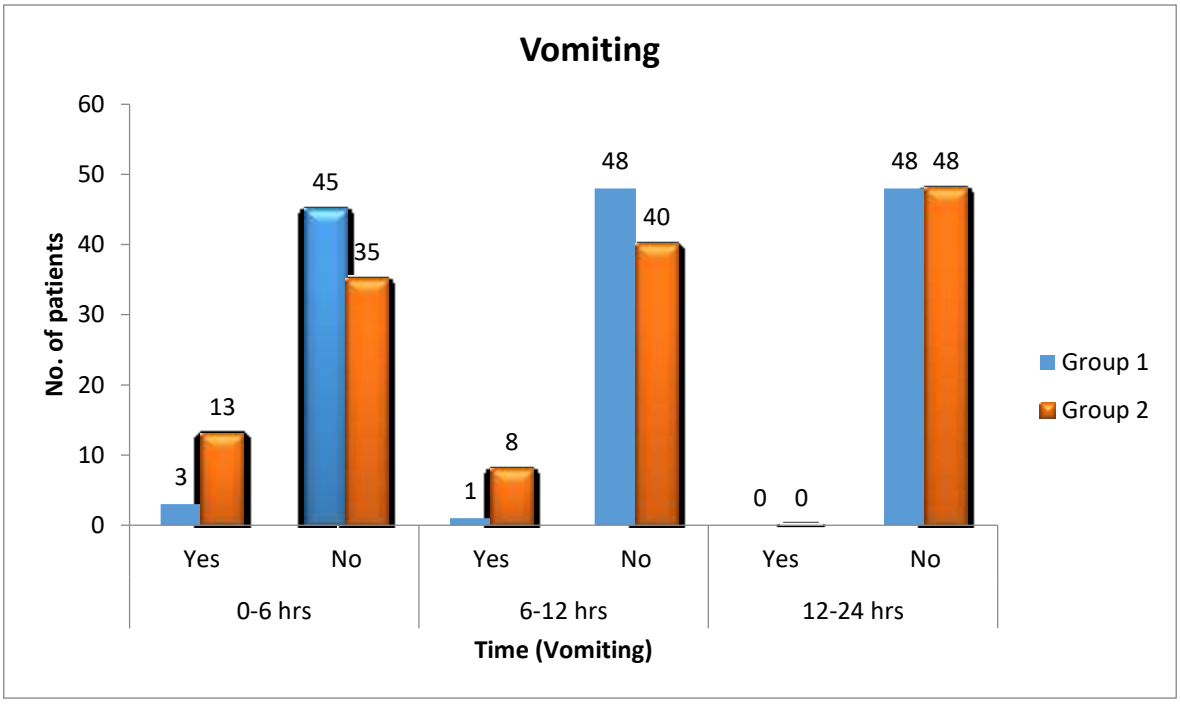

Nausea
No. of patients
60
50
40
30
20
10
0
6
28
42
20
2
10
46
38
0
1
48
47
Yes
No
Yes
No
Yes
No
0-6 hrs
6-12 hrs
12-24 hrs
Time (Nausea)
Group 1
Group 2

Table 8: Number of Patients with Experienced different levels of Vomiting Categories at different Time points

Time		Vomiting				p value
		Group 1		Group 2		
		N	%	N	%	
0-6 hrs	Yes	3	6.25	13	27.08	**0.006**
	No	45	93.75	35	72.92	
6-12 hrs	Yes	1	2.08	8	16.67	**0.030**
	No	47	97.92	40	83.33	
12-24 hrs	Yes	0	0.00	0	0.00	NA
	No	48	100.00	48	100.00	

Chi square & Fisher exact test used.

Table 8: shows the Number of Patients experienced different levels of vomiting categories at different time points. Vomiting incidences were noted at different time points from 0 to 6 hrs; 6-12 hrs and 12-24 hrs. It was observed that out of the total 48, 3 patients (6.25%) under group 1 experienced vomiting between 0-6 hr. While in group 2, 13 patients (27.08%) experienced vomiting in the time period of 0-6 hrs. In the time period of 6 to 12hr , 1 patient (2.08%) out of the 48 and in group 2 , 8 out of 48 patients had vomiting. Further in time period of 12-24hrs , none of the patients in both group 1 and group 2 had episode of vomiting. P value was significant for time period of 0-6hr and 6-12 hr , while for 12-24hr it came as insignificant.


Vomiting
No. of patients
60
50
40
30
20
10
0
3
13
45
35
1
8
48
40
0
0
48
48
Yes
No
Yes
No
Yes
No
0-6 hrs
6-12 hrs
12-24 hrs
Time (Vomiting)
Group 1
Group 2

DISCUSSION

One of the most unpleasant and quite common complications experienced by a patient undergoing anaesthesia and surgery is the Postoperative nausea and vomiting. Several factors including the prolonged use of CO2 insufflation, intraoperative use of isoflurane, female gender , postoperative use of opioids , prior history of PONV or motion sickness , obesity and other factors such as hypotension, manipulation of abdominal viscera[71] are identified as some of the risk factors in the cause of PONV. However, there is no clear understanding about the common sequel of general anaesthesia and the etiology of nausea and vomiting after laparoscopic surgeries.The complication of PONV needs to be addressed as the patients who had undergone prior surgeries and had suffered from PONV in those surgeries , the unpleasant experience lasts forever and often makes them anxious later in any future surgeries during the perioperative period. To address this complication and to reduce the incidence of PONV following LC , a multitherapy approach is needed , as sole antiemetic though has reduced the incidence of PONV but not to a level of satisfaction.

Therefore the current study was designed as randomised comparative study between two groups with group 1 receiving Ondansetron plus dexamethasone and group 2 receiving Ondansetron for PONV in Laproscopic Cholecystectomy surgeries. Study revealed that in comparison between the two groups , Ondansetron plus Dexamethasone group (Group 1) patients showed lesser incidence of postoperative nausea and vomiting(PONV).

Studies earlier shown that the use of selective $5HT_3$ receptor antagonists such as Ondansetron as effective medication for the treatment and prevention of PONV in the laparoscopic cholecystectomy.[60] However, several other studies have also been reported that most of the antiemetic including ondansetron are not entirely effective in all patients. Our study is being supported by previous study by L. LÓPEZ-OLAONDO et al., (1996) where it was concluded that ondansetron as well as dexamethasone alone provided adequate control of ponv but the combination group (Ondansetron +Dexamethasone) was most effective in reducing PONV than when given alone. Bhattarai B et al (2011) in his study concluded that combination of dexamethasone with ondansetron is more effective than ondansetron alone. Lalit Kumar et al and Vinit kumar et al (2016-2017) in their study

concluded that Dexamethasone and Ondansetron when given alone are equally effective. But to overcome the adverse event of ponv at deepest level a multi-therapy approach is needed.

Hence the concept of combination therapy is greatly needed. In agreement with the above, several studies have been conducted to control PONV with various combination therapy.[59,60,68,70] However, studies have seldom reported a consistent observation rather showing significant variabilities, which might be due to the use of different types and time duration of surgery. Therefore an attempt was made in our present study to determine the effect of Dexamethasone in combination with ondansetron to patients undergoing laparoscopic cholecystectomy and compared the results observed from patients treated with ondansetron alone.

The dose of 4 mg of Ondansetron used in our current study was chosen based on several of the earlier studies where the select dose of Ondansetron was determined to prevent PONV after Cesarean delivery, laparoscopic and day care surgery[59,60,64] .Dose of 4 mg Ondansetron was chosen in this study both alone and in combination with Dexamethasone 8 mg , because either 4 mg or 8 mg is equally effective in the prophylaxis of PONV and both doses are reported to be equally safe after rapid iv administration in terms of the Cardiovascular adverse effects. In a study by J. I. Tzeng et al with 120 parturients who received epidural morphine 3 mg, Dexamethasone 8 mg IV significantly decreased the incidence of PONV compared with saline and droperidol (51% and 21%,respectively).[72] There is substantial evidence that Dexamethasone, alone or in combination with Ondansetron, may possess antiemetic effects during the postoperative period. Whereas 8 mg dose of dexamethasone is being used for prophylaxis of PONV in adult population after general surgery and chemotherapy as well.

The incorporation of 4 mg Ondansetron combination with dexamethasone 8 mg may offers a more cost-effective option as well. Dexamethasone 8 mg plus the use of Ondansetron 4 mg antiemetic combination costs less than 8 mg Ondansetron alone. If patients are not at risk of drug interaction because of polypharmacy, it is reasonable to take the cost effectiveness into account. Dexamethasone has a long biological half-life of 36 to 72 hours and is suggested to provide better control of delayed PONV (i.e.,beyond 24 hours). Ondansetron a specific 5-hydroxytryptamine 3 antagonist, has been shown to decrease the incidence of PONV associated with elective Cesarean delivery.

In the present study we have observed that intravenous administration of Dexamthasone 8

mg in combination with Ondansetron 4 mg to patients who were undergoing laparoscopic cholecystectomy showed a significantly decreased incidence of PONV on comparison with patients treated with 4mg of Ondansetron alone. Overall from 0 to 24 hrs, incidence of PONV in the patients treated with the combination of 8 mg of Dexamethasone and 4 mg of Ondansetron was less in comparison with the incidence observed in patients treated with 4 mg of Ondansetron alone. This is in concurrence with the previous studies where the combination group has beneficial effects apart from preventing PONV.

In our study 12.50% patients of group 1 showed nausea and 58.33% of patients showed nausea in time period of 0-6 hr , p value (<0.0001) is significant . Secondly 4.17% patients in group 1 and 20.83% patients in group 2 had nausea between the time period of 6 to 12 hrs , p value (0.027) is significant. During 0-6 hr period , out of 6 patients who had nausea in group 1 ,1 patient had mild nausea (16.66%) and 5 patients (83.3%) had moderate nausea whereas in group 2 out of 28 patients who had nausea , 8 patients (28.57%) had mild nausea , 17 patients (60.7%) had moderate nausea , 3 patients (10.71%) had severe nasuea. During 6-12hr period , out of 2 patients who had nausea in group 1 , 1 patient(50%) had mild nausea and 1 patient (50%) had moderate nausea wheras in group 2 , out of 10 patients who had nausea , 7 patients (70%) had mild nausea and 3 (30%) had moderate nausea. During 12-24hr period , none of the patients had nausea in group 1 whereas as 1 patient had nausea in group 2 which was moderate on scaling.

In our study vomiting was also observed to be significantly less in the combination group as compared to solo anti emetic prophylaxis. Similarly, in a study by Basant Bhattarai et al (2011) , he found that a combination of Dexamethasone and ondansetron is more effective as prophylaxis for postoperative nausea and vomiting with overall incidence of 8% as compared to 24% with ondansetron alone.[60] They suggested that delayed PONV (2-24 hours) was better controlled. A combination of Dexamethasone and Ondansetron treatment is more effective in PONV prophylaxis, complements previous studies.

Henzi et al and colleagues in their systematic review concluded that currently best available prophylaxis for PONV is a combination of dexamethasone and 5-HT3 receptor antagonist.[73] There was a higher incidence of PONV among the females as compared to the males which is in concurrence with earlier studies. In our study patients only experienced mild side effects which did not require any active intervention.

Our study showed that patients in the Dexamethasone and Ondansetron groups required

less analgesia than those receiving monotherapy. The possible mechanism may be mediated by the afferent nerve fibers that mediate pain, which are a subset of polymodal C-nociceptors, and their transmission to the central nervous system is enhanced by prostaglandins. Dexamethasone inhibits PGE2 synthesis and may provide analgesia by this mechanism. Ondansetron is also implicated in central processing of pain.

In our current study, consumption of decreased analgesics in the patients treated with Dexamethasone plus Ondansetron might be due to the analgesic properties of both these drugs.

Based on the observations made in our study we could conclude that intravenous administration of Dexamethasone plus Ondansetron in the prophylaxis of PONV for patients undergoing laparoscopic cholecystectomy was more effective than the Ondansetron alone as the standard antiemetic therapy, which is associated with a frequent failure of PONV prophylaxis.

SUMMARY

The gold standard technique used for the treatment of gallstones disease nowadays is laparoscopic cholecystectomy. It has several advantages like smaller incision, reduced blood loss, and reduced postoperative stay and pain. However it is a type of procedure which are prone for PONV. Experience of PONV is very much distressing for a patient. To achieve a better control of PONV a multi-therapy approach is needed , as use of single drug therapy for controlling PONV have not reduced the incidences to a desired level. The Randomised comparative study titled "Randomised comparative study to determine/compare the efficacy of Ondansetron in combination with Dexamethasone and by alone in preventing PONV of patients undergoing elective laparoscopic cholecystectomy under general anaesthesia" was planned and conducted in the Department of Anaesthesiology at Santosh Medical College and Hospital, Ghaziabad, UP. After the approval from Institutional ethics committee of Santosh deemed to be University, Ghaziabad, and obtained informed consent from the patients those who were admitted for elective laparoscopic cholecystectomy the study was conducted for a period of one year. About 96 patients admitted for elective laparoscopic cholecystectomy aged between 18 to 60 years of either sex , ASA physical status I & II were randomly assigned in groups of 48 each.

96 patients were randomly divided into two groups:

Group 1 – Patients receiving Ondansetron + Dexamthasone (n = 48)
Group 2 – Patients receiving Ondansetron alone (n =48)

The drugs were injected 5 minutes before induction. Anaesthetic management was standardized. Vital parameters were monitored intraoperatively, and furthermore, the nausea, vomiting and pain were monitored at time intervals of 0-6hr; 6–12hr; and 12 -24hrs postoperatively. Necessities of the rescue analgesics, additional antiemetic and any other postoperative complications were also monitored. The values obtained on various parameters over the period from the two study groups were compared and the statistical significance were calculated.

The data collected during the study was compiled using a Microsoft Excel spread sheet and analyzed statistically using the statistical package for the MedCalc statistical Software version 20.115 for window editions.

The demographic data and the vitals have not shown any significant difference between the two groups. However, the postoperative nausea and vomiting were observed to be lower in the Ondansteron and Dexamethasone combination group of patients when compared to the patients who received ondansetron alone for prophylaxis . Thus from the observed results it can be concluded that the combination treatment of Ondansetron with Dexamethasone would be more efficacious in controlling and/or preventing postoperative nausea and further with less requirement of the rescue antiemetic for the patients undergoing elective laparoscopic cholecystectomy under general anaesthesia.

CONCLUSION

Through the observed results it can be concluded that the combination of Ondansetron with Dexamethasone would be more efficacious in controlling and/or preventing postoperative nausea and vomiting (PONV) along with lesser requirement of the rescue antiemetic , for the patients undergoing elective laparoscopic cholecystectomy under general anaesthesia.

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ANNEXURES 1

PROFORMA

1. GENERAL INFORMATION-

NAME	
AGE (yrs)	
SEX(M/F)	
OCCUPATION	
ADDRESS	
DIAGNOSIS	
OPERATION PROPOSED	
MRD No.	
DATE	

2.GENERAL EXAMINATION-

GENERAL CONDITION	
HEART RATE	
BLOOD PRESSURE	
TEMPERATURE	
SPO2	
MOUTH OPENING	
MPG GRADE	

NECK MOBILITY	
ORAL EXAMINATION	
ASA GRADE	

3. SYSTEMICEXAMINATION-

SYSTEM	FINDINGS
RESPIRATORY SYSTEM	
CARDIOVASCULAR SYSTEM	
CENTRAL NERVOUS SYSTEM	
PER ABDOMEN	

4. ANY SYSTEMIC DISEASE-

5. INVESTIGATIONS-

Complete blood counts

Blood sugar (Random)

Viral Markers

Bleeding time

LFT

Clotting time

Blood urea

Serum creatinine

Urine -routine, microscopy

Chest x-ray

Serum electrolytes

ECG

6. INTRA ABDOMINAL PRESSURE:

7. CO2 FLOW RATE:

8. ETCO2(in range):

9. Any complication:

10. Duration of surgery:

11. Numerical score for Nausea :

- 0 = No Nausea.
- 2-3 = mild
- 4 = moderate
- 5 = Nausea as bad as can be.

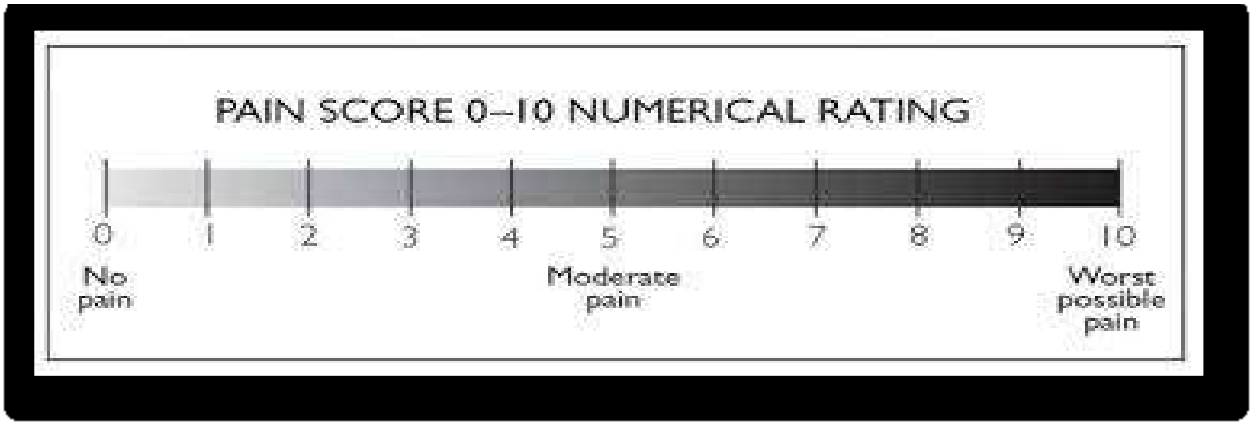
Early nausea – 0 to 6 hr postoperatively

Delayed nausea – 6 to 24hr postoperatively

12. For Vomiting :

- If Present - Yes
- If Absent = NO

13. NRS SCORE:



HOUR	ABDOMINAL PAIN	RIGHT SHOULDER PAIN
0		
2		
4		
6		
12		
24		

12. POSTOPERATIVE VITALS-

Hour	SBP	DBP	MAP	HR	SPO_2	NAUSEA	VOMITING
0							
6							
12							
24							

ANNEXURE 2

DEPARTMENT OF ANAESTHESIA

SANTOSH MEDICAL COLLEGE & HOSPITAL

GHAZIABAD, U.P

I am being requested to take part in a study entitled

"A prospective randomised controlled study for evaluation of high-volume low-concentration intraperitoneal ropivacaine for post-laparoscopic cholecystectomy analgesia"

VOLUNTARY PARTICIPATION

My participation in the study is entirely voluntary and I am free to with draw from the study as and when I feel so.

INFORMED CONSENT FORM

I _____ son/daughter/wife of _____ resident of_____ give my full, free and voluntary consent to be included as a subject in the study entitled "A prospective randomised controlled study for evaluation of high-volume low-concentration intraperitoneal ropivacaine for post-laparoscopic cholecystectomy analgesia" I have been explained, in my own language, and to my full satisfaction, the aim and nature of the study and risks and benefits. I have also been explained that my confidentiality will be maintained and all the investigations/ interventions will be carried out only after my consent is obtained. I am aware of my right to opt out of the study at any point without giving any reason, and without penalty or loss of routine care benefits.

Patient's/ Patient's relative's signature Doctor's Signature:
Or thumb impression.

Name: Date:

We have witnessed that the patient signed the above form in the presence of his free will after fully understanding its content.

Signature of Witness

Name:

Signature of Investigator

Name:

ANNEXURE 3

संतोषमेडिकलकॉलेजएवंअस्पताल (गाजियाबाद)

सूचितसहमति

मैं_____बेटा_____निवासी_____

_____ घोषणा करता हूं कि मैं डॉ._____, ने मेरी भाषा में अपने अध्ययन, अध्ययन के उद्देश्य के बारे मे, और अध्ययन के दौरान अपनाई जानेवाली विभिन्न प्रयोगशाला जांच के बारे में सूचित कर दिया है। मुझे अध्ययन की अवधि और उस के दौरान अपनाए जानेवाले निर्देश भी मेरी भाषा मे समझा दिए गए हैं| मैं उपरोक्त अध्ययन में बिना किसी दबाव के दाखिला ले रहा हूं और पूर्ण सहमति दे रहा हूं| सन्तोषअस्पताल, गाजियाबाद में अपने आगे के उपचार पर बिना प्रतिकूल प्रभाव डाले इस अध्ययन से और प्रयोगशाला जांच की प्रकृति से मैं जब चाहूँ बाहर जाने के अपने अधिकार को सुरक्षित रख रहा हूं I

रोगी / रोगी के रिश्तेदार के हस्ताक्षर डॉक्टर के हस्ताक्षर या अंगूठे का निशान

नाम

नांक:

मेरी उपस्थिति में मरीज ने पूरी तरह से डाकटर के बताए गए अध्ययन और निर्देशों को समझने के बाद अपनी स्वतंत्र इच्छा से ऊपरके फार्म पर हस्ताक्षर कि ए हैं

Signature of Investigator

ANNEXURE 4

LIST OF ABBREVIATIONS

1. LC- LAPAROSCOPIC CHOLECYSTECTOMY
2. DVT - DEEP VENOUS THROMBOSIS
3. PE- PULMONARY EMBOLISM
4. LA – LOCAL ANESTHETIC
5. NSAID- NON STEROIDAL ANTI INFLAMMATORY DRUGS
6. CO2 – CARBON DIOXIDE
7. PONV- POST OPERATIVE NAUSEA VOMITING
8. I M- INTRA MUSCULAR
9. I V – INTRA VENOUS
10. CNS – CENTRAL NERVOUS SYSTEM
11. VAS SCORE- VISUAL ANALOG SCORE
12. NMDA – N-METHYL D-ASPARTATE
13. PVB- PARA VERTEBRAL BLOCK
14. TAP – TRANVERSE ABDOMINAL PLANE
15. BRILMA – BLOCKING OF BRANCHES OF INTERCOSTAL NERVE AT THE LEVEL OF MID AXILLARY LINE
16. HR- HEART RATE
17. SBP – SYSTOLIC BLOOD PRESSURE
18. DBP – DIASTOLIC BLOOD PRESSURE
19. MAP – MEAN ARTERIAL PRESSURE
20. DOA- DURATION OF ANALGESIA
21. SPO2 – OXYGEN SATURATION
22. ETCO2 - END TIDAL CARBON DIOXIDE
23. I P – INTRAPERITONEAL
24. STP – SHOULDER TIP PAIN
25. DOS – DURATION OF SURGERY
26. NRS – NUMERIC RATING SCALE
27. TENS – TRANSCUTANEOUS ELECTRIC NERVE STIMULATION
28. ASA – AMERICAN SOCIETY OF ANAESTHESIOLOGY

ETHICAL COMMITTEE CLEARANCE

SANTOSH
Deemed to be University
(Established u/s 3 of the UGC Act, 1956)

F. No. SU/2021/1830[41] Dated: 17.07.2021

Subject: Grant of Ethical Clearance for Thesis Protocol Topic **"A RANDOMISED COMPARATIVE STUDY BETWEEN ONDANSETRON AND DEXAMETHASONE FOR PREVENTING POST OPERATIVE NAUSEA & VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY."**, submitted by **Dr. Vashist Raj,** MD/MS student of Batch 2020-2021, Department of **Anaesthesia**.

*****

With reference to his/her request for grant of Ethical Clearance for the Thesis Protocol entitled **"A RANDOMISED COMPARATIVE STUDY BETWEEN ONDANSETRON AND DEXAMETHASONE FOR PREVENTING POST OPERATIVE NAUSEA & VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY."**, **Dr. Vashist Raj** is informed that the Thesis Protocol submitted by him/her was considered by the **Screening Committee** of the Santosh Medical College & Hospital in its meetings held on 19.03.2021, 22.03.2021, 24.03.2021, 25.03.2021, 26.03.2021, 27.03.2021 and 06.04.2021. The recommendations of the **Screening Committee** were considered in detail by the Institutional **Ethics Committee** in its meeting held on **12.07.2021** and the same was **approved** by the **Ethics Committee**.

He /She is informed accordingly for further necessary action.

[Dr. V. P. Gupta]
REGISTRAR

SANTOSH DEEMED TO BE UNIVERSITY REGISTRAR GHAZIABAD, NCR INDIA

Dr. Vashist Raj
MD/MS student of batch 2020-2021
Department of Anaesthesia
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Copy to:

1. The Vice Chancellor
2. The Dean, SMC&H
3. The Dean – Research
4. The Dean – Academics
5. The Director – IQAC
6. Guide of the Student
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